Implications for the Human Genome Project on the Management of Renal Cell Carcinoma

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* I have no disclosures related to this CME event
Is This an Indolent Tumor?
Could we have predicted this event?
Can We Predict Treatment Response

Neoadjuvant TKI

Dec 2006

Mar 2007
• Single institution, open-label, non-randomized
  – Biopsy proven clear cell RCC
  – cT2-T3b N0 M0 (all patients had cT3a tumors)
  – 24 patients

• Neoadjuvant Axitinib
  – 5 mg BID with upward titration (10 mg BID)
  – 12 weeks continuous therapy (off 36 hours prior to radical or partial nephrectomy)
• Response in 100% of tumors (23 patients)
  – Median reduction in diameter 28.3%
    • Median 10 cm → 6.9 cm
  – No progression while on therapy
Can We Optimize Therapeutic Strategies

*IVC Tumor Thrombus*


Sunitinib

x 2 cycles

Level IV – Intra-atrial

Level I-II - Infrahepatic

Pre-operative TKI

IVC Tumor Thrombus

Can We Optimize Systemic Therapies?

March 2010

Feb 2012
Can We Optimize Systemic Therapies?

Mar 2010

Feb 2012
Optimizing Systemic Therapies?

March 2010

Feb 2012
There are Success Stories Using Current Decision Tools!!

But, are we too often rolling the dice?
Current Tools for Determining Prognosis/Treatment for Kidney Cancers

• Post treatment prognosis
  – SSIGN
  – UCLA Integrated Staging System (UISS)
  – Karakiewicz Nomogram

• Cytoreductive nephrectomy
  – Culp Criteria

• Metastatic patients
  – Motzer criteria
### SSIGN Score for Clear Cell RCCA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T Stage</strong></td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>0</td>
</tr>
<tr>
<td>pT2</td>
<td>1</td>
</tr>
<tr>
<td>pT3a</td>
<td>2</td>
</tr>
<tr>
<td>pT3b</td>
<td>2</td>
</tr>
<tr>
<td>pT3c</td>
<td>2</td>
</tr>
<tr>
<td>pT4</td>
<td>0</td>
</tr>
<tr>
<td><strong>N Stage</strong></td>
<td></td>
</tr>
<tr>
<td>pNx</td>
<td>0</td>
</tr>
<tr>
<td>pN0</td>
<td>0</td>
</tr>
<tr>
<td>pN1</td>
<td>2</td>
</tr>
<tr>
<td><strong>M Stage</strong></td>
<td></td>
</tr>
<tr>
<td>pM0</td>
<td>0</td>
</tr>
<tr>
<td>pM1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Tumour size</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>0</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nuclear Grade</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>0</td>
</tr>
<tr>
<td>present</td>
<td>2</td>
</tr>
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</table>

Frank et al., J Urol. 2002;168:2395-2400
Overall Survival for RCCA
UCLA Integrated Staging System (UISS)
Overall Survival for RCCA
UCLA Integrated Staging System (UISS)
# Overall Survival for RCCA

## UCLA Integrated Staging System (UISS)

<table>
<thead>
<tr>
<th></th>
<th>NM at Diagnosis (n=468)</th>
<th>M at Diagnosis (n=346)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>No. Patients</td>
<td>128</td>
<td>190</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>100</td>
<td>97.2</td>
</tr>
<tr>
<td>2 year</td>
<td>98.8</td>
<td>90.6</td>
</tr>
<tr>
<td>3 year</td>
<td>94.9</td>
<td>87.7</td>
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<tr>
<td>4 year</td>
<td>93.1</td>
<td>85.5</td>
</tr>
<tr>
<td>5 year</td>
<td>91.1</td>
<td>80.4</td>
</tr>
</tbody>
</table>

Note: Standard Error not shown

(Zisman et al., JCO, Dec, 2002)
Karnofsky Performance Status

• 100  Normal no complaints; no evidence of disease
• 90   Able to carry on normal activity; minor signs or symptoms of disease
• 80   Normal activity with effort; some signs or symptoms of disease
• 70   Cares for self; unable to carry on normal activity or to do active work
• 60   Requires occasional assistance, but is able to care for most of his personal needs
• 50   Requires considerable assistance and frequent medical care
• 40   Disabled; requires special care and assistance
• 30   Severely disabled; hospital admission is indicated although death not imminent
• 20   Very sick; hospital admission necessary; active supportive treatment necessary
• 10   Moribund; fatal processes progressing rapidly
• 0    Dead
Motzer Criteria

1. Low Karnoksky PS (≤ 70)
2. High LDH > 1.5x normal
3. Low Hgb < lower limit of normal
4. High corrected serum calcium > 10.0
5. Absence of prior nephrectomy
6. Presence of liver mets
7. Increased alkaline phosphatase

Motzer RJ et al, J Clin Oncol, 2002, 20:289 (460 patients treated with IFN-alpha alone as initial therapy)
Motzer Criteria

• Low risk
  – 0 risk factors, median survival 30 months

• Intermediate risk
  – 1-2 risk factors, median survival 14 months

• Poor risk
  – > 3 risk factors, median survival 5 months

• Criteria developed during cytokine era

What do These Models Have in Common?

- Readily available patient characteristics
- Readily available tumor characteristics
- No tumor specific markers
- Is current practice a “personalized approach”? 
- Still seems quite rudimentary in 2015 
- Can we do better?
An Ongoing Struggle With Cancers
....including kidney cancers

“If the only tool you have is a hammer, you tend to see every problem as a nail.”

Abraham Maslow
Traditional treatment model for many cancers (including RCCA): Like trying to fit a square peg into a round hole!! Tumors might appear the same, but tumor biology, response to therapy, etc., is very heterogeneous.
### Renal Cell Cancer – Histological Subtypes

<table>
<thead>
<tr>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
<th>Papillary Type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VHL</td>
<td>cMET</td>
<td>FH cMYC</td>
<td>BHD</td>
<td>BHD</td>
</tr>
</tbody>
</table>

BHD, Birt-Hogg-Dubé; VHL, von Hippel-Lindau.

<table>
<thead>
<tr>
<th>Malignant Histology</th>
<th>Frequency</th>
<th>Origin</th>
<th>Genetic Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>70-80%</td>
<td>Proximal convoluted tubule</td>
<td>3p25 (VHL)</td>
</tr>
<tr>
<td>Papillary type I</td>
<td>5%</td>
<td>Distal convoluted tubule</td>
<td>7q-31 (c-Met)</td>
</tr>
<tr>
<td>Papillary type II</td>
<td>10%</td>
<td>Distal convoluted tubule</td>
<td>1q42 (FH)</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>5%</td>
<td>Distal convoluted tubule</td>
<td>multiple (incl. 17p)</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>&lt;1%</td>
<td>Collecting duct</td>
<td>Monosomy (1,6,14,15,22)</td>
</tr>
<tr>
<td>Medullary</td>
<td>&lt;1%</td>
<td>Collecting duct</td>
<td>sickle cell</td>
</tr>
</tbody>
</table>
An “explosion” of new information and strategies!!
The Cancer Genome Atlas (TCGA)

- TCGA project began in 2005
- Primary aim:
  - Catalogue genetic mutations responsible for the development of cancer using high throughput genome sequencing techniques to improve our ability to diagnose, treat and prevent cancer
- Supervising bodies:
  - National Cancer Institute
  - National Human Genome Research Institute
- Funded by the US government
The Cancer Genome Atlas (TCGA)

• Initial focus towards three malignancies:
  – GBM, Lung and Ovarian CA
• Goal: characterize 20-25 tumors
• Up to 500 different patient tumor samples
  – Obtained prior to adjuvant therapies
• Whole-genome and exome sequencing sequencing reveals:
  – Every tumor has different mutations
  – Mutations drive tumor biology
Comprehensive Molecular Characterization of Clear Cell RCCA

- 346 Collaborators from numerous institutions
- Tumors from 446 patient assayed - at least one molecular platform:
  - RNA sequencing
  - DNA methylation arrays
  - miRNA sequencing
  - SNP arrays
  - Exome sequencing
  - Reverse phase protein arrays
- Genetic changes underlying clear cell RCCA:
  - alterations in genes (i.e. VHL) controlling cellular oxygen sensing
  - maintenance of chromatin states (i.e. PBRM1)

Comprehensive Molecular Characterization of Clear Cell RCCA

• Identified 19 significantly mutated genes
• Potential therapeutic targets:
  – PI3K/Akt/mTOR pathway recurrently mutated (altered in ~28% of tumors)
• Widespread DNA Hypo/hypermethylation:
  – HYPO - associated with mutation of methyltransferase SETD2
  – HYPER – associated with tumors of higher stage and grade
• Crosstalk between pathways:
  – Mutations of chromatin remodeling complex (i.e. PBRM1) affect other pathways

Comprehensive Molecular Characterization of Clear Cell RCCA

- Aggressive cancers associated with metabolic shift:
  - Down-regulation of genes involved in the TCA cycle
  - Decreased AMPK and PTEN protein levels
  - Up-regulation of the pentose phosphate pathway and the glutamine transporter genes
  - Increased acetyl-CoA carboxylase protein
  - Altered promoter methylation of miR-21 and GRB10

- Potential opportunities for disease treatment
mRNA & miRNA Patterns Reflect Molecular Subtypes of Clear Cell RCCA
BAP1 & PBRM1 Mutations

- **BAP1 and PBRM1:**
  - Two-hit tumor suppressor genes
  - Regulate seemingly different gene expression programs
  - Mutations are mutually exclusive

- **BAP1 Mutations:**
  - Present in 15% of clear-cell renal cell carcinomas
  - Associated with high nuclear grade, stage and tumor aggression when compared with tumors exclusively mutated for PBRM1

- **PBRM1 Mutations:**
  - Present in 50% of clear-cell renal cell carcinomas

- **Combined loss of BAP1 and PBRM1 genes**
  - Present in small percent (<5%) of tumors
  - Some reports reveal association with rhabdoid features

Molecular Characterization of RCCA with BAP1 & PBRM1 Mutations

Figure A: Risk of metastases over time since surgery.

Figure B: Risk of death from RCC over time since surgery.

BAP1 & PBRM1 Mutations in Non-Clear Cell RCCA

- 458 patients treated surgically for ccRCC, pRCC, chRCC
- IHC to evaluate PBRM1 and BAP1 protein expression
- Loss of PBRM1 and BAP1 staining:
  - Clear cell = 43% (80/187) and 10% (18/187)
  - Papillary = 3% (2/59) and 0% (0/61)
  - Chromophobe = 6% (1/17) and 0% (0/17)
- Loss of PBRM1 or BAP1 are key events in ccRCC, whereas other pathways may support tumorigenesis in non-ccRCC subtypes

Take Home Messages

• “Tip of the Iceberg” as it relates to the Molecular Characterization of Renal Cell Carcinomas

• Some mutations are ubiquitous in renal tumors (i.e. VHL, PBRM1), whereas some are only present in a subset of cancer cells within the same tumor (i.e. BAP1, SETD2)
  – Implications for core biopsy results and interpretations

• Early results of genome–wide sequencing establish a foundation for an integrated pathological and molecular genetic classification of RCC
  – *Paves the way for subtype-specific treatments exploiting genetic vulnerabilities*